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PATENT SPECIFICATION

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(54) OPHTHALMIC COMPOSITIONS AND CONTACT LENS DISINFECTING COMPOSITIONS

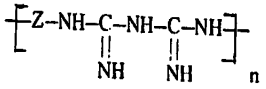
(71) We, SMITH & NEPHEW RESEARCH LIMITED, a British Company, of Gilston Park, Harlow, Essex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to compositions for use in connection with the eye and with contact lenses.

Compositions for use in connection with the eye and with contact lenses which are subsequently placed in the eye are desirable such as to avoid discomfort and damage to the eye. Certain antibacterial compositions currently in use employ low molecular weight bactericides which if used in connection with hydrophilic soft contact lenses may be absorbed and concentrated in the lens. Such a lens when placed in the eye can release a concentrated solution leading to irritation of the eye.

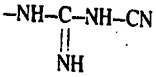
It has been found that certain polymeric bactericides may be used in concentrations such that the problem with soft hydrophilic contact lenses is greatly alleviated. These polymeric bactericides may also be used in compositions for hard contact lenses and for use as eye drops.

According to the present invention an ophthalmic composition or a contact lens disinfecting composition comprises an aqueous solution of at least one ophthalmically acceptable polymeric diguanide of the formula:



I

in which each end of the polymeric diguanide is independently terminated either by an amino group or by an



group and in which Z represents an organic divalent bridging group which may be the same or different throughout the polymer, n is at least 3, (preferably from 3 to 80 and more preferably from 3 to 30) and/or at least one ophthalmically acceptable salt thereof, the diguanide and/or its salt being present in a total amount of from 0.0005 to 0.05% by weight based on the total weight of the composition. The individual polymeric diguanides cannot normally be isolated easily and it is therefore usual to use a mixture of such diguanides. Preferably the average molecular weight of the diguanides in such mixtures is of the order of 900 to 1600 corresponding to an average value of n of about 4 to 8.

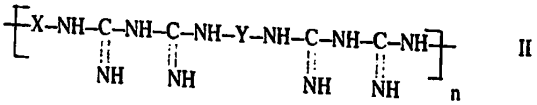
Preferably the solution is isotonic or substantially isotonic with tear fluid.

Preferably the solution has a pH of from 5.0 to 8.0, more preferably from 6.5 to 7.5. If desired the composition may be buffered to a pH of from 5.0 to 8.5, preferably 6.5 to 7.5.

The composition of the invention is preferably such as to cause no irritation or other adverse ocular changes when used in the eye.

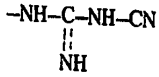
The bridging groups Z may be the same or different throughout the molecule and may be aliphatic, cyclo-aliphatic, aromatic or heterocyclic radicals. Preferably each Z is a polymethylene chain, optionally interrupted by oxygen or sulphur atoms and optionally incorporating saturated or unsaturated cyclic nuclei.

Where Z is not the same throughout the molecule the polymeric diguanide is preferably of the formula:



II

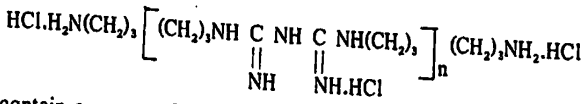
in which each end of the polymeric diguanide is independently terminated either by an amino group or by an



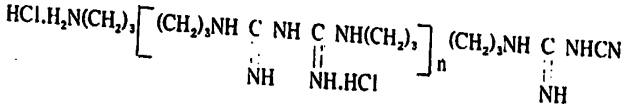
group and in which X and Y each represents an organic divalent bridging group and n is from 4 to 40 or an opthalmically acceptable salt thereof, the solution containing from 0.0005% to 0.05% by weight of diguanide or its salt, being isotonic with tear fluid and being buffered to a pH of between 5.0 and 8.0. Preferably the total number of carbon atoms contained in X and Y together which are directly interposed between adjacent nitrogen atoms in the polymer chain is greater than 9 and smaller than 17. In those cases where the radicals X and/or Y incorporate one or more cyclic groups the number of carbon atoms directly interposed between adjacent nitrogen atoms is calculated on the basis of the shortest path between the nitrogen atoms. The preferred value for both X and Y is the hexamethylene radical.

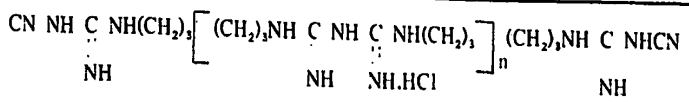
Polymeric diguanides of the general formula I are described in British Patents Specifications Nos. 702,268; and 1,152,243 together with processes for their preparation, and it is envisaged that all the polymeric diguanides described in these two Specifications and which fall within the scope of general formula I given above may be used in the compositions of the invention.

Particularly preferred is a mixture of polyhexamethylene diguanides in the form of their hydrochlorides and having an average molecular weight from 900 to 1600. One such mixture of polyhexamethylene diguanide hydrochlorides is sold as an aqueous solution by I.C.I. under the Trade Name Vantocil 1B ("Vantocil" is a registered Trade Mark). Vantocil 1B is a 20% aqueous solution of the hydrochloride of a mixture of polyhexamethylene diguanides having an average molecular weight between 900 and 1600 i.e. a compound of the general formula I in which Z represents a hexamethylene radical throughout and the average value for n is between 4 and 8. The amount of Vantocil 1B used is adjusted to give a total amount of the diguanide hydrochlorides in the composition of from 0.0005 to 0.05% by weight. In one embodiment the Vantocil 1B is present in the composition in an amount of at least 0.005g. per 100 mls of final solution. Vantocil 1B is considered to be a mixture of diguanides of the formula:—



and may contain amounts of compounds of the formula:—





The compositions of the invention may also include one or more additional ingredients selected from the following:

Additional bactericides e.g.	thiomersal benzalkonium chloride and phenyl mercuric salts, and other ophthalmic preservatives.
Thickening Agents e.g.	polyvinyl alcohol, carboxy-methylcellulose and hydroxy ethylcellulose, and other ophthalmically acceptable agents of this type.
Non-ionic surfactants e.g.	products sold under the Trade Name Tween and Pluronic ("Tween" and "Pluronic" are registered Trade Marks).

Ophthalmic drugs may be added to the compositions of the invention, in which case the compound of general formula I acts as a preservative for the drug solution. Suitable ophthalmic drugs include miotic drugs, for example pilocarpine; mydriatic drugs; anti-infective agents, e.g. chloramphenicol; and anti-inflammatory agents, e.g. steroids.

Where the composition of the invention contains additional ingredients these may be in solution in the water or may be dispersed in the water or, together with the water, may form an emulsion. The diguanide however is present in the aqueous phase.

The preferred amount of the compound of the general formula I present in the compositions of the invention is dependent upon the strength and activity of the particular compound selected and upon the particular use of this composition. When used for soft contact lenses the composition preferably contains from 0.0005 to 0.0025%, more preferably 0.00125%, by weight of the polymeric diguanide and/or its salt. When used for hard contact lenses the composition preferably contains 0.001 to 0.01% by weight of the polymeric diguanide and/or its salt and when used as eye drops this composition preferably contains 0.0025 to 0.05% by weight of the polymeric diguanide and/or its salt.

The invention will now be further described by way of reference to the following Examples:—

EXAMPLE 1.

The following ingredients were mixed together to form a solution:

	% by weight
Polyhexamethylene diguanide hydrochloride	0.00125
Sodium chloride	0.64
Potassium chloride	0.14
Disodium Hydrogen Phosphate	0.24
Potassium dihyrogen phosphate	0.06
Distilled water	to make up to 100%

The resultant solution was isotonic with tear fluid, and had a pH of 7.2 and the composition was found to be useful for the storage of soft hydrophilic contact lenses.

EXAMPLE 2.

The following ingredients were mixed together to form a solution:

	% by weight
Polyhexamethylene diguanide hydrochloride	0.00125
Sodium chloride	0.78
Potassium chloride	0.17
Distilled water	to make up to 100%

The resultant solution was isotonic with tear fluid and the composition was found to be useful for the storage of soft hydrophilic contact lenses.

EXAMPLE 3.

The following ingredients were mixed together to form a solution:

	% by weight
Polyhexamethylene diguanide hydrochloride	0.00125
Sodium Chloride	0.78
Potassium chloride	0.17
Disodium E.D.T.A.	0.1
Distilled water	to make up to 100%

The resultant solution was isotonic with tear fluid, and the composition was found to be useful for the storage of soft hydrophilic contact lenses.

EXAMPLE 4.

The following ingredients were mixed together to form a solution:

	% by weight
Benzalkonium chloride	0.004
Polyhexamethylene diguanide hydrochloride	0.005
Sodium chloride	0.9
[1]Hydroxy ethyl cellulose	0.5
[2]Poly vinyl alcohol	2.0
Distilled water	to make up to 100%

1 — Natrosol 250 M (50—100 cp grade) marketed by Hercules Powder
2 — Elvanol 51—05 (87.5 — 89.5 hydrolysed) marketed by Dupont

The resultant solution was isotonic with tear fluid and the composition was found to be useful for the storage and wetting of hard contact lenses.

EXAMPLE 5.

The following ingredients were mixed together to form a solution:

	% by weight
Polyhexamethylene diguanide hydrochloride	0.005
*Pluronic L 64	0.8
Di sodium EDTA	0.2
Di sodium Hydrogen Phosphate	0.85
Potassium di Hydrogen Phosphate	0.175
Distilled water	to make up to 100%

*Pluronic L 64 is a non ionic surfactant based on Polyoxyethylene-Polyoxypropylene Block copolymer and is marketed by Wyandotte Chemical Corporation.

The resultant solution was isotonic with tear fluid, and had a pH of 7.0 and the composition was found to be useful for the soaking and cleaning of hard contact lenses.

EXAMPLE 6.

The following ingredients were mixed together to form a solution:

	% by weight
Polyhexamethylene diguanide hyrochloride	0.01
$Ha_2 HPO_4$	0.2
KH_2PO_4	0.1
Na Cl	0.157
K Cl	0.183
Na Acetate $3H_2O$	1.0
Water to make up	100 mls.

The resultant solution was isotonic with tear fluid, and had a pH of 7 and the composition was found to be useful as eyedrops either with or without the addition of an ophthalmic drug.

EXAMPLE 7.

The following ingredients were mixed together to form a solution:

	% by weight
Pilocarpine hydrochloride	2.0
Polyhydroxymethylene diguanide hydrochloride	0.005
Benzalkonium chloride	0.005
Water to make up	100 mls.

The resultant solution could be thickened to 20 cp, could be buffered up to a pH of 5 and was found to be useful for the treatment of glaucoma.

EXAMPLE 8.

The following ingredients were mixed together to form a solution:

	% by weight
Polyhexamethylene diguanide hydrochloride (.0.05 mls. of a 20% solution of Vantocil IB)	0.01
Tween 20	1.00
Na_2HPO_4	0.68
KH_2PO_4	0.34
Na Cl	0.40
Water to make up	100 mls.

The resultant solution was isotonic with tear fluid, and had a pH of 7 and the composition was found to be useful for the storage of hard contact lenses and for use in the eye either with or without the addition of an opthalmic drug.

In the Examples above and in the tests described below the polyhexamethylene diguanide hydrochloride referred to was used as Vantocil IB. The percentages quoted are however amounts of this active ingredient i.e. the polyhexamethylene diguanide hydrochloride.

Tests were carried out to ascertain the bactericidal activity and the irritant response of solutions of the invention.

I. BACTERIOCIDAL ACTIVITY

To 20 mls of each of the test preparations was added an inoculum of 0.2 mls of the test micro organism to give a fixed concentration of 10^6/ml. At timed intervals after innoculation, one ml samples were taken in duplicate and added to a neutralising medium. The medium was incubated for 7 days at 37°C and any growth in this medium was identified. The neutralising medium was nutrient broth (OXOID — "OXOID" is a registered Trade Mark) containing 0.5% W/V Tween 80 and 0.1% W/V lecithin or 0.1% Juramin and was shown to effectively neutralise the antibacterials used in the study by effecting the recovery of approximately 10 organism inoculum.

The standard used for acceptance of ophthalmic solutions as being adequately preserved in the microbiological laboratory is that the solution reduced a population of Staph. aureus NCTC 6571, E. coli NCTC 86 and Ps. aeruginosa NCTC 6750 by six decades within an hour.

RESULTS In the following table failure of the test is indicated by F and a pass by P.

No.	Test solution*	Results
I	Aqueous solution containing 0.000625% by weight polyhexamethylene diguanide hydrochloride	P
II	Aqueous solution containing 0.0075% chlorohexidine acetate	P
III	As II but 0.005% chlorohexidine acetate	F
IV	Aqueous solution containing 0.005% benzalkonium chloride	F

* All solutions buffered to approximately pH 7.0 and made isotonic with tear fluid.

It can be seen from the above that polyhexamethylene diguanide is effective at much lower concentrations than either of the other two materials included for comparison purposes.

In order to test the capacity to withstand repeated challenges, the standard "die off" challenge was repeated on the 0.00125% solution of polyhexamethylene diguanide hydrochloride of Example 1 on five successive days. The capacity of the solution did not appear to change from the initial challenge to that of the final fifth day challenge. 20 ml samples of the contaminated solution were filtered after this fifth day challenge and no organism could be isolated.

2. IRRITANCY TESTS

Soft lens storage solutions containing different bactericides were tested for their potential irritancy to the eye.

The irritant response was assessed in Rabbits fitted with soft hydrophilic lenses of lightly cross linked polyhydroxyethyl methacrylate.

Each lens was pretreated by alternate storage in 5 ml of the test solution and 5 ml of physiological saline for periods of 3 hours repeated three times.

The pretreated lenses were worn for 6 hours daily and stored overnight in 5 ml of the test solution.

Reactions such as Corneal Opacity Conjunctival Vascularisation, irites and chemosis were assessed daily according to the F.D.A. Scheme. Whenever irritation was observed the eyes were stained with fluorescein and the progress of recovery recorded.

RESULTS

Test No.	*Formulation Containing	Treatment terminated on day	Irritancy Assessment	Symptoms	Degree of corneal involvement	Time required for recovery (days)
V	0.005% Benzalkonium chloride+disodium edetate	1	Severe	Corneal opacity Gross injection	Total, entire cornea stained	8
VI	0.0025% Benzalkonium chloride+disodium edetate	3	Severe	Chemosis of eyelids Discharge	Severe	5
VII	0.0025% Vantocil	21	Moderate	Slight to moderate injection Chemosis Iritis	Minimal	5
VIII	0.00125% Vantocil	28	Minimal	Slight injection	None	1
IX	0.01% Chlorhexidine diacetate	1	Severe	Gross injection Chemosis	Total complete imprint of lens shown by fluorescein staining	2
X	0.005% Chlorhexidine acetate	21	Severe	Moderate injection Chemosis Corneal opacity	Moderate	(3) One eye shows a persistent corneal opacity
XI	0.1% Chlorocresol	1	Severe	Gross injection Chemosis Iritis	Total entire cornea stained	Not recovered within 28 days observation
XII	0.2% Chlorocresol	1	Severe	Corneal opacity & neovascularisation	Total, entire cornea stained	

* All solutions buffered to approximately PH 7.0 and made isotonic with tear fluid.

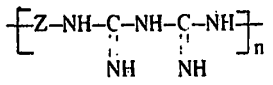
It can be seen from the above that the solutions of the invention i.e. those of tests VII and VIII perform better than the other solutions included for comparative purposes.

A further test was carried out by instilling 0.1 mls of the composition of Example 6 into the conjunctival sac of the left eye of six albino rabbits. Treatment continued daily for 21 days, and reactions were graded according to the F.D.A. scheme. No irritant response was observed at any time.

The invention also includes a method of disinfecting a contact lens which comprises contacting the contact lens with a composition of the invention.

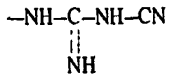
WHAT WE CLAIM IS:—

1. An opthalmic composition or a contact lens disinfecting composition comprising an aqueous solution of at least one ophthalmically acceptable polymeric diguanide of the formula:



I

in which each end of the polymeric diguanide is independently terminated either by an amino group or by an



group and in which Z represents an organic divalent bridging group which may be the same or different throughout the polymer and n is at least 3, and/or at least one opthalmically acceptable salt thereof, the diguanide and/or its salt being present in a total amount of from 0.0005 to 0.05% by weight based on the total weight of the composition.

2. A composition as claimed in claim 1 in which n is from 3 to 80.

3. A composition as claimed in claim 2 in which n is from 3 to 30.

4. A composition as claimed in any one of the preceding claims, in which a mixture of polymeric diguanides of formula I and/or their salts is used.

5. A composition as claimed in claim 4, in which the average molecular weight of the diguanides in the mixture is from 900 to 1600.

6. A composition as claimed in any one of the preceding claims which is isotonic or substantially isotonic with tear fluid.

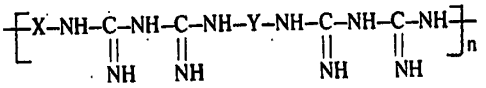
7. A composition as claimed in any one of the preceding claims which has a pH of from 5.0 to 8.0.

8. A composition as claimed in claim 7, which has a pH of from 6.5 to 7.5.

9. A composition as claimed in claim 7 or 8, in which the composition is buffered to the stated pH.

10. A composition as claimed in any one of the preceding claims, in which each Z is a polymethylene chain, optionally interrupted by oxygen or sulphur atoms and optionally incorporating saturated or unsaturated cyclic nuclei.

11. A composition as claimed in any one of the preceding claims in which the polymeric diguanide is of the formula:



II

in which X and Y each represents organic divalent bridging groups.

12. A composition as claimed in any one of the preceding claims in which the polymeric diguanide comprises a mixture of polyhexamethylene diguanides in the form of their hydrochlorides and having an average molecular weight from 900 to 1600.

13. A composition as claimed in any one of the preceding claims, which also includes one or more additional ingredients selected from the following:— bactericides, thickening agents, non-ionic surfactants and ophthalmic drugs.

14. A composition as claimed in claim 13, which contains benzalkonium chloride as an additional bactericide.

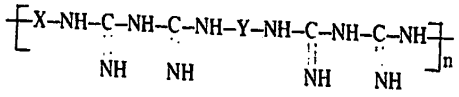
15. A composition as claimed in any one of claims 1 to 14 for use with soft hydrophilic contact lenses, which contains from 0.0005 to 0.0025% by weight of polymeric diguanide and/or its salt.

16. A composition as claimed in claim 15, which contains 0.00125% by weight of polymeric diguanide and/or its salt.

17. A composition as claimed in any one of claims 1 to 14 for use with hard contact lenses, which contains 0.001 to 0.01% by weight of the polymeric diguanide and/or its salt.

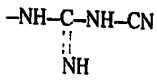
18. A composition as claimed in any one of claims 1 to 14 for use as eye drops, which contains 0.0025 to 0.05% by weight of the polymeric diguanide and/or its salt.

19. An ophthalmic composition or a contact lens disinfecting composition comprising an aqueous solution of an ophthalmically acceptable polymer diguanide of the formula:



II

in which each end of the polymeric diguanide is independently terminated either by an amino group or by an



group and in which X and Y each represents an organic divalent bridging group and n is from 4 to 40 or an ophthalmically acceptable salt thereof, the solution containing from 0.0005% to 0.5% by weight of diguanide or its salt, being isotonic with tear fluid and being buffered to a pH of between 5.0 and 8.0.

20. A composition as claimed in claim 19, which has a pH of from 6.5 to 7.5.

21. A composition as claimed in claim 19 or 20, which also includes one or more additional ingredients selected from the following; bactericides, thickening agents, non-ionic surfactants and ophthalmic drugs.

22. A composition as claimed in claim 21 which contains benzalkonium chloride as an additional bactericide.

23. A composition as claimed in any of claims 19 to 22 in which the diguanide is in the form of an aqueous solution of the hydrochlorides of a mixture of polyhexamethylene diguanides having an average molecular weight between 900 and 1600.

24. A composition as claimed in claim 23, in which a 20% aqueous solution of the hydrochlorides is present in the composition in an amount of from at least 0.005g. (i.e. 0.001g. of diguanide salt) per 100 mls of final solution.

25. A composition as claimed in claim 1 substantially as hereinbefore described in any one of Examples 1 to 7.

26. A composition as claimed in claim 1 substantially as hereinbefore described in Example 8.

27. A method of disinfecting a contact lens which comprises contacting the lens with a solution as claimed in any one of claims 1 to 18 or 25.

28. A method of disinfecting a contact lens which comprises contacting the lens with a composition as claimed in any one of claims 19 to 22.

29. A method of disinfecting a contact lens which comprises contacting the lens with a solution as claimed in claim 23 or 24.

30. A method of disinfecting a contact lens which comprises contacting the lens with a solution as claimed in claim 26.

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